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Review Article

Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials

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Abstract

Background. Morphine, and analgesics other than morphine (AOM), are commonly used to treat postoperative pain after major surgery. However, which AOM provides the best efficacy-safety profile remains unclear.
Methods. Randomized trials of any AOM alone or any combination of AOM compared with placebo or another AOM in adults undergoing major surgery and receiving morphine patient-controlled analgesia were included in a network meta-analysis. The outcomes were morphine consumption, pain, incidence of nausea, vomiting at 24 h and severe adverse effects.
Results. 135 trials (13,287 patients) assessing 14 AOM alone or in combination were included. For all outcomes, comparisons with placebo were over-represented. Few trials assessed combinations of two AOM and none the combination of three or more. Network meta-analysis found morphine consumption reduction was greatest with the combination of two AOM (acetaminophen + nefopam, acetaminophen + NSAID, and tramadol + metamizol): -23.9 (95% CI -40;-7.7), -22.8 (-31.5;-14) and -19.8 (35.4;-4.2) mg per 24 h, respectively. For AOM used alone, morphine consumption reduction was greatest with α-2 agonists, NSAIDs, and COX-2 inhibitors. When considering the risk of nausea, NSAIDs, corticosteroids and α-2 agonists used alone were the most efficacious (OR 0.7 [95% CI: 0.6-0.8], 0.36 [0.18-0.79], 0.41 [0.15-.64], respectively). The paucity of severe adverse effects data did not allow assessment of efficacy-safety balance.
Conclusions. A combination of aetaminophen with either an NSAID or nefopam was superior to most AOM used alone, in reducing morphine consumption. Efficacy was best with three AOM used alone (α-2 agonists, NSAIDs and COX-2 inhibitors) and least with tramadol and acetaminophen. There is insufficient trial data reporting adverse events.
Clinical trial registration. PROSPERO: CRD42013003912.

Key words: analgesics; balanced analgesia; postoperative pain; surgery; systematic review

Editor's Key Points

- A network meta-analysis analyses treatment effects across studies that did not conduct direct head-to-head comparisons.
- This analysis confirmed morphine-sparing with some combinations of non-opioid drugs.
- Morphine-sparing analgesic techniques can reduce the risk of postoperative nausea and vomiting.
- Adverse event reporting must be included when conducting clinical trials.

More than 230 million major surgeries are performed annually in the world.[1] Severe pain after surgery remains a major problem, occurring in 20% to 40% of patients.[2] Administration of morphine by patient-controlled analgesia (PCA) has extensively improved the management of postoperative pain,[3] and can be considered a gold standard to alleviate pain after major surgery.[4] Among analgesics, morphine is considered the reference agent but it has limits: moderate efficacy on relieving pain during movement, side-effects such as nausea and vomiting, which can be incapacitating for the patient and delay postoperative rehabilitation.

Balanced analgesia was proposed 25 yr ago to improve postoperative management;[5] it is based on a combination of different analgesic drugs to reduce pain while decreasing the postoperative use of morphine and associated side-effects.[6–8] Therefore, non-opioid analgesics and weak opioids (defined as analgesics other than morphine [AOM]) are often used alone or in combination along with morphine PCA after major surgery.

Many randomized trials and meta-analyses have compared the effects of AOM monotherapy combined with morphine, to that of placebo on pain and postoperative nausea and vomiting (PONV).[9–17] However, few trials have compared these AOM against each other, few trials have assessed AOM combination regimens, and few meta-analyses have synthesized the adverse-effect profile of AOM. As a consequence, which AOM has the best efficacy-safety balance when combined with morphine is unclear.

We undertook a systematic review with network meta-analysis of randomized controlled trials that compared AOM to a placebo or another AOM for treating pain after major surgery. We assessed clinical efficacy and safety using network meta-analysis to integrate data from direct and indirect comparisons,[18–21] thereby determining the relative efficacy and safety of all treatments against each other.

Methods

Data sources and search strategy

The study was registered at PROSPERO (CRD42013003912). We searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and LILACS databases for reports of randomized trials included from the inception of each database to August, 2015, with no limits on publication language, date, or status. The search equation is available in Supplementary data 1. We also searched the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects for previous relevant systematic reviews. We hand-searched the annual conference proceedings of the American Society of Anesthesiology and European Society of Anaesthesiology from June 2008 to June 2015 and searched for completed trials in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. We systematically contacted primary authors and manufacturers for studies with incomplete data.

Study selection

We included all trials involving adults who underwent major surgery as defined by Earl[22] and who received morphine by PCA for a least 24 h that compared at least one AOM to a placebo or another AOM. Treatment classes of interest were AOM with systemic administration, whatever the timing, dose, route and mode of administration (single or multiple bolus, continuous). Eligible AOM classes included 1) nonsteroidal anti-inflammatory drugs (NSAIDs) 2) COX-2 inhibitors, 3) acetaminophen, 4) tramadol, 5) nefopam, 6) metamizol, 7) corticosteroids and 8) α-2 agonists. Trials assessing the combination of these drugs were eligible. We included trials comparing one drug to two different doses or the timing of administration (pre- or post-incision) of another drug, or one drug to two other drugs in the same class. In such trials, we grouped the arms assessing different doses or timings of administration, or different drugs of the same class.

We excluded trials in which 1) continuous morphine infusion was administered in addition to PCA, 2) PCA involved an opioid other than morphine, 3) PCA was used for less than 24 h, 4) regional analgesia was used in addition to PCA, or 5) an anti-hyperalgesic was used. We also excluded trials of surgery requiring postoperative ventilation during the first 24 h. Finally, we excluded reports authored by Reuben who allegedly fabricated data.[23]

Two pairs of authors independently screened titles, abstracts and full manuscripts according to the selection criteria. Any disagreement was discussed with a third author until consensus was reached.

Data extraction and risk of bias assessment

After developing a data extraction form, we tested it on 20 included studies selected at random and refined it accordingly. Pairs of reviewers independently extracted data from each study. Disagreements were resolved by consensus with a statistician. We extracted information about the trial setting (country), participants (age, gender, weight), type of surgery (abdominal, gynaecologic, orthopedic, mixed), treatments (drug, dose, route, mode and timing of administration) and outcome measures. Drug doses were converted to number of defined daily doses as established by the WHO and corresponding to the average maintenance dose per day, for a drug used for its main indication in adults (Supplementary data Table 1).[24] Two independent reviewers assessed trial methodological quality by using the Cochrane Risk of Bias tool, with any discrepancies resolved by consensus.[25]

Outcome measures

The co-primary outcomes were cumulative morphine consumption (in milligrams of morphine equivalent) and pain (on a 100-mm visual analog scale [VAS]), both at 24 h. Pain scores reported on a numerical rating scale were converted to a 100-mm VAS. The secondary outcomes were the occurrence of nausea and of vomiting at 24 h. If 24-h data were not available, we used the data point closest to 24 h. Because many articles did not report the occurrence of nausea and vomiting separately, we used the